66. The method of Claim 65, wherein the increased amount of caspase results from increased conversion of procaspase to caspase.

67. The method of Claim 65, wherein the increased amount of caspase results from increased oligomerization of the caspase.

68. The method of Claim 45, wherein the enhanced procaspase or caspase activity results from prolonging the duration of the activity.

69. The method of Claim 45, wherein the enhanced procaspase or caspase activity results from increasing the amount of procaspase or caspase.

70. The method of Claim 69, wherein the increased amount of caspase results from increased conversion of procaspase to caspase.

71. The method of Claim 69, wherein the increased amount of caspase results from increased oligomerization of the caspase.---

REMARKS

Prior to entry of this Amendment C, Claims 41, 45 and 53-63 are pending in this application. No claim is allowed.

In this Amendment, Claims 41 and 45 have been amended, Claims 53-62 have been cancelled and new Claims 64-73 have been added. The cancellation and amendment of the claims is for the purpose of more particularly pointing out and clarifying the subject matter which Applicants regard as their invention, and for the purpose of expediting prosecution. The cancellation and amendments should not be construed as agreement with or acquiescence to any of the pending rejections.

Support for the amendments and new claims can be found throughout the specification, the claims and the figures as originally filed. Specifically, support for the amendments to Claims

41 and 45 can be found at least in the specification at page 3, line 26. Support for new Claims 64 and 68 can be found at least in the specification at page 39, line 18. Support for new Claims 65 and 69 can be found at least in the specification at page 39, line 19. Support for new Claims 66 and 70 can be found at least in the specification at page 38, line 33. Support for new Claims 67 and 71 can be found at least in the specification at page 39, line 1. No new matter has been added to the application by the amendments or by the addition of these new claims.

Telephonic Interview

Applicants' Attorney thanks Examiner Bansal for the helpful telephonic interview of October 3, 2000 in which the present Office Action was discussed.

Withdrawal of Rejection of Claims 41 and 45 Under 35 USC §112, Second Paragraph

The withdrawal by the Examiner of the rejection of Claims 41 and 45 under 35 USC §112, second paragraph is gratefully acknowledged.

Rejection of Claims 41, 45 and 53-63 Under 35 USC §103(a)

Claims 41, 45 and 53-63 stand rejected under 35 USC §103(a) as being unpatentable over Fearnhead *et al.*, "An Interleukin-1β-Converting Enzyme-like Protease is a Common Mediator of Apoptosis in Thymocytes", *FEBS Lett.*, 375: 283-288 (1995).

Specifically, the Examiner states at page 2-3:

> Fearnhead et al teach that caspases are involved in apoptosis in thymocytes. Fearnhead et al also teach an assay method whereby this caspase activity in thymocytes was assayed by a method wherein thymocytes were incubated with dexamethasone, thapsigargin, etoposide which are all activators of apoptosis, and wherein apoptosis was assessed by monitoring cell death...The conclusion that apoptosis was mediated by caspases in thymocytes was reached by Fearnhead et al by including inhibitors of caspases and assessing an inhibition of apoptosis in these cells. Thus, Fearnhead intrinsically teaches that agents such as dexmethasone, thapsigargin and others as mentioned can increase the activity of thymocyte caspases. In fact Fearnhead also indicates (page 287, column 1, last

paragraph) that TLCK was an agent that could function as an enhancer of apoptosis induced by most stimuli.

Although Claims 53-63 have been cancelled in this Amendment, the subject matter contained in those claims is contained in new Claims 64-71. Thus, the following discussion is applicable to all the pending claims. Applicants specifically traverse the rejection of the claims on the grounds that Fearnhead *et al.* neither teach nor suggest a method of enhancing procaspase or caspase activity, of identifying an agent which enhances procaspase or caspase activity, or the desirability of identifying such an agent.

To develop a model of an apoptosis pathway, Fearnhead *et al.* combined compounds known to induce apoptosis, for example, dexamethasone, thapsigargin and etoposide, with ICE-like protease inhibitors and measured the effect on certain indicators of apoptosis in thymocyte cells. Fearnhead *et al.* were particularly interested in ascertaining the stages at which the studied inhibitors blocked the apoptotic process (page 283, column 2, last full paragraph). Fearnhead *et al.* concluded that the stages of the apoptotic pathway in thymocytes were regulated by multiple proteases (page 287, column 1, first full paragraph). Fearnhead *et al.* also concluded that apoptosis induced by different stimuli was inhibited/potentiated differentially by TLCK and Z-VAD.FMK (page 287, column 1, last full paragraph).

It appears that the Examiner has taken the position that the compounds utilized by Fearnhead *et al.* to induce apoptosis, for example, dexamethasone, thapsigargin and etoposide, must also necessarily be agents which enhance procaspase or caspase activity. Applicants respectfully note that the Examiner's conclusion is not supported by the teachings of the Fearnhead *et al.* reference.

The Fearnhead *et al.* cell-based study demonstrated that apoptosis induced by known stimuli was inhibited by, for example, Z-VAD.FMK. However, Fearnhead *et al.* neither teaches nor suggests that the compounds used to induce apoptosis affect an isolated caspase. Moreover, Fearnhead *et al.* neither teaches nor suggests measuring the effect on apoptosis of the enhancement of the activity of an isolated procaspase or caspase, nor identifying an agent which enhances that activity. Therefore, the teachings of Fearnhead *et al.* fail to provide the ordinarily skilled artisan with a reasonable expectation of success in developing a method of identifying an agent which enhances the activity of a procaspase or caspase. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 41, 45 Under 35 USC §112, Second Paragraph

Claims 41, 45 and 53-63 are newly rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner stated that Claims 41 and 45 were ambiguous with regard to the dependent Claims 53-63, that clarification of the term "prolonged" was required for Claims 56 and 61, and that Claims 57 and 62 failed to further limit the scope of their respective parent claims.

Claims 53-62 have been cancelled and the subject matter contained in those claims has been placed in new Claims 64-71. The cancellation and amendment of the claims is for the purpose of more clearly conveying in the claims the teachings contained in the specification that an agent can enhance the activity of a procaspase or a caspase by prolonging the duration of the activity of the procaspase or caspase or by increasing the amount of available procaspase or caspase. Dependent Claims 66-67 and 70-71 further limit Claims 65 and 69, respectively, by specifying different ways in which the available amounts of procaspase or caspase can be increased.

Applicants believe that the claims, as amended, even more particularly point out and distinctly claim the subject matter of Applicants' invention. Therefore, it is respectfully requested that the rejection be reconsidered and withdrawn.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Lisa M. Treannie

Lisa M. Treannie
Registration No. 41,368
Telephone (781) 861-6240
Facsimile (781) 861-9540

Lexington, Massachusetts 02421-4799

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